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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/937,057	02/26/2002	Antoine F Carpentier	249326USOX PCT	4658

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EXAMINER	
ZARA, JANE J	

ART UNIT	PAPER NUMBER
1635	

NOTIFICATION DATE	DELIVERY MODE
04/19/2007	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Advisory Action Before the Filing of an Appeal Brief	**Application No.** 09/937,057	**Applicant(s)** CARPENTIER, ANTOINE F	
	Examiner Jane Zara	**Art Unit** 1635	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 28 February 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: *21*.
   Claim(s) objected to: _____.
   Claim(s) rejected: *1-6,22 and 23*.
   Claim(s) withdrawn from consideration: *7-20 and 25-29*.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Please see Attachment.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____
13. ☐ Other: _____.

JZ one TC1600

JANE ZARA, PH.D.
PRIMARY EXAMINER

Attachment

Claims 1-6, 22 and 23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record set forth in the Office actions mailed 3-6-06 and 11-29-06.

The claims are drawn to oligonucleotides for the targeted alteration of any genetic sequences in a plant, which oligonucleotides comprise a DNA domain having at least one mismatch with respect to any target genetic sequence to be altered, wherein the alteration confers herbicide resistance by introducing a site specific mutation conferring herbicide resistance.

Applicant's arguments filed 2-28-07 have been fully considered but they are not persuasive. Applicant argues that written description for this broad genus, encompassing a vast myriad of sequences, is presumed to be adequate unless a preponderance of evidence is presented as to why the instantly claimed genus is not adequately described. The genus encompassing any oligonucleotide sequence between 17-240 nucleotides that contains one mismatch with respect to any plant genetic sequence to be altered, and which alteration generates a site specific mutation conferring herbicide resistance, embraces a vast array of sequences that one of ordinary skill in the art could not envision the concise structures that would distinguish them from other existing sequences outside of the instantly claimed genus. The sequences provided in the instant application are not representative of the genus comprising any oligonucleotide containing any mismatch with respect to any plant

genetic sequence to be altered which, upon targeted alteration of a plant genetic sequence, generates a site specific mutation conferring herbicide resistance.

As pointed out previously to Applicant, Yoon et al speaks to the inability to readily identify members of the broad genus claimed, encompassing oligonucleotide sequences that function in a predictable manner for targeted gene alteration (Nature Biotech., Vol. 20, pages 1197-1198, 2002). "It may... be possible to develop selection strategies for oligodeoxynucleotide-based gene targeting that overcome the low frequency of gene conversion." (p. 1198, center column). "Progress in gene repair requires the identification of cellular components and rate-limiting step[s] involved in gene conversion to develop methodical selection procedures. ...given the prevalent skepticism generated by the poor reproducibility of results by different groups..." (p. 1198, last paragraph).

See also Albuquerque-Silva et al (Nature Biotech., Vol. 19, page 1011, 2001): "In reviewing the 20 original studies published on chromosomal gene conversion using RDOs, we found none fulfilling all four of our criteria. In view of potential artifacts and the lack of reproducibility of published reports, we consider that conversion mediated by chimeric RDOs still awaits validation." (last paragraph on p. 1011).

Contrary to Applicant's assertions, the citations of record, articulating the doubts expressed by the skilled artisans Albuquerque-Silva and Yoon, indeed satisfy the burden of evidence required to rebut the presumption that Applicant was in possession of this vast genus of oligonucleotides claimed.

Claims 1-6, 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Moerschell et al (Proc. Natl. Acad. Sci., Vol. 85, pages 524-528, 1988) and Holmes et al (Proc. Natl. Acad. Sci., Vol. 87, pages 5837-5841, 1990), the combination in view of the combined teachings of Hirschberg et al (USPN 5,792,903), Bennett et al (USPN 6,387,699) and Nicolaides et al (USPN 6,982,169) insofar as the claims are drawn to compositions and methods comprising the administration of single stranded oligonucleotides for targeted alteration of a genetic sequence in vitro and in plants comprising a single stranded oligonucleotide having a DNA domain with at least one mismatch with respect to the genetic sequence to be altered and further comprising 2'-O-methyl, locked nucleotide analog and/or phosphorothioate internucleotide modifications, wherein herbicide resistance is generated by the site specific mutation for reasons of record set forth in the Office action mailed 11-29-06.

Applicant's arguments filed 2-28-07 have been fully considered but they are not persuasive. Applicant argues that the obviousness rejection is improper because the reliance upon Bennett for the routine incorporation of modifications that enhance oligonucleotide stability is improper since antisense oligonucleotides fail to direct targeted gene alteration. But, contrary to Applicant's assertions, Bennett is not being relied upon for the use of antisense oligonucleotides as substrates in target gene alteration as instantly claimed. Bennett is relied upon for the well known methods of incorporating stabilizing modifications into oligonucleotides.

It was well established in the art, prior to filing the instant application, that the modifications previously taught by Bennett et al were routinely incorporated into

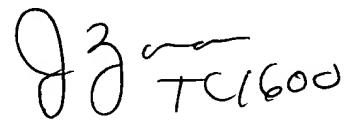
oligonucleotides and were well known in the art to prevent nuclease degradation of nucleic acids. It is therefore a reasonable assumption that the lack of degradation of oligonucleotides by nuclease digestion will make the intact oligonucleotides more available for reactions in a test tube or in a cell, including for mutatgenesis reactions, for target gene binding, and for other types of gene inhibition reactions. It is therefore unclear why Applicant asserts that this aspect of the obviousness rejection is incorrect. If a molecule is not degraded, it will remain present for longer periods of time in a reaction mixture, and will be available at higher concentrations for whatever reactions utilize it as a substrate (or even in some instances as a catalyst). Therefore its concentration will remain higher in a modified form than under conditions where it would be degraded (e.g. in unmodified form). For these reasons, it would have been obvious to utilize routinely modified oligonucleotides, with enhanced stability from nuclease degradation, in targeted gene alteration reactions. The instant rejection is maintained.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
4-8-07



JANE ZARA, PH.D.
PRIMARY EXAMINER